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Phenoxybenzamine in Septic Shock

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DIMINISHED blood flow to vital structures appears to be the common denominator of clinical shock states. As blood pressure is one of the few objective measurements available, there has been a tendency to treat this parameter empirically by infusion of fluids (the obvious and proper treatment for hypovolemic shock), and by using vasopressors to raise blood pressure and thereby increase tissue perfusion. In some instances of treated hypovolemic shock and in certain cases of septic shock, administration of fluids or vasopressors produces no helpful response but rather a course of progressive deterioration characterized by decreasing tissue perfusion, measured by cardiac output, rising plasma lactate, falling blood pressure and urinary output, hypoxemia, a tendency toward metabolic acidosis, respiratory dysfunction, coagulation disorders, and rising central venous pressure. Proper attention to volume replacement should be the first consideration in the management of all cases of shock and is the only treatment necessary in most cases. This principle is applicable to shock due to many precipitating factors, but usually excludes cardiogenic shock secondary to myocardial infarction.

Numerous case reports in the literature document the existence and frequency of the septic shock syndrome since it was first described by Borden in 1951.^{4, 13, 20, 25} Al-

though primary interest has been in shock associated with gram-negative organisms, septic shock may also complicate infections due to other microbials, including gram-positive cocci, which liberate exotoxins rather than endotoxins.¹⁹

The characteristics of the hemodynamic abnormality in septic shock are poorly understood. Primarily on the basis of animal studies a variety of therapeutic regimens have been devised to correct hemodynamic changes that result from overwhelming sepsis. These measures include vasopressors to support blood pressure, replacement of blood volume, pharmacologic doses of corticosteroids, administration of aldosterone, administration of hyperbaric oxygen and the use of inotropic drugs such as isoproterenol. The continuing high mortality rate in septic shock and the lack of quantitative clinical data attest to the fact that additional knowledge is required in evaluating therapy in the human.

Increasing awareness of the importance of tissue perfusion rather than blood pressure stimulated Nickerson to propose the use of vasodilators in shock.²¹ Protective reflex sympathetic vasoconstriction redistributes flow to maintain perfusion in the heart and brain. Although vasoconstriction supports arterial blood pressure, tissue capillary perfusion is severely compromised. The importance of maintaining capillary flow provides the theoretical basis for the use of vasodilating agents in the treatment of shock.¹³ Although profound reduction in tissue perfusion in septic shock

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is established clinically, the responsible mechanisms are unknown. Conceivably, alterations in vascular reactivity to catecholamines constitute an important contributory mechanism.^{9, 10, 21, 30}

It is generally accepted that agents inhibiting sympathetic vasoconstriction can protect against a fatality in animals subjected to endotoxin shock^{15, 16} but there have been few reports dealing with intravenously administered vasodilators in man. In fewer instances has the published material supporting the use of vasodilators in shock been substantiated by hemodynamic and laboratory data. To evaluate the usefulness of phenoxybenzamine in the treatment of clinical shock, the condition being treated must be clearly defined.

This paper presents studies on five young patients who were admitted to the Shock Unit of the Walter Reed General Hospital for shock which was refractory to conventional resuscitative measures. In four patients the etiology of the shock syndrome appeared to be solely septicemia with no evidence of hypovolemia or primary myocardial disease. The fifth patient had bilateral pheochromocytomata and his clinical course was characterized by intense vasoconstriction and fulminant pulmonary edema. These patients were treated with phenoxybenzamine and their clinical courses were studied in detail. The series includes all patients who have received

phenoxybenzamine at the Walter Reed Shock Unit.

Clinical Material

For the past 12 months a Shock Study Unit has been maintained at Walter Reed Hospital for the physiologic observation and intensive treatment of critically ill patients in shock. Most patients treated during this period had unrecognized volume deficits with associated biochemical disorders, sepsis with associated volume deficits, or primary cardiorespiratory failure. Four of the patients, all under the age of 33, developed refractory shock believed to be solely based on septicemia. Each patient had been intensively treated by conventional methods of volume replacement, large doses of antibiotics, correction of acid-base imbalances, and corticosteroids. All had been given vasopressors as a last resort to restore blood pressure and tissue perfusion. These patients progressively deteriorated on this regimen and were considered to be in imminent danger of death. Clinical data are listed in Table 1.

In the history and on physical examination special attention was paid to level of consciousness, skin color, fingernail capillary perfusion, temperature, character of pulse, skin turgor and moisture, and respiratory rate. A Teflon catheter was inserted into the surgically exposed radial artery for measurement of systemic arterial

TABLE 1. *Clinical Summary*

No.	Pt.	Sex	Age	Diagnosis	Blood culture	Outcome
1	D. C.	M	32	Localized peritonitis post-peritoneoscopy	Klebsiella-Aerobacter	Survived
2	J. N.	M	30	Pneumonia	Pneumococcus	Survived
3	A. C.	F	31	Calculus with pyelonephritis	E. coli	Survived
4	S. L.	F	26	Endometritis	None. E. coli from vagina & culdocentesis	Died on 13th day of respiratory complications
5	W. H.	M	22	Bilateral pheochromocytomata	None	Died on 4th day of respiratory complications

blood pressure and withdrawal of arterial blood samples. Central venous pressure was monitored through a large polyethylene catheter introduced percutaneously by a supraclavicular approach into a subclavian vein and threaded under fluoroscopic control into the superior vena cava. In three patients an N.I.H.-type cardiac catheter was threaded from the basilic vein into the main pulmonary artery under fluoroscopic control and allowed to remain in place for intervals up to 72 hours. Intravascular pressures were monitored with strain gauge transducers* and a carrier wave amplification and recording system.** Serial indicator-dilution curves to determine cardiac output were made by injecting indocyanine green dye from calibrated syringes into the central venous catheter followed immediately by a saline flush. Constant aspiration at 21.9 mm./min. from the radial artery was accomplished by a constant-speed withdrawal pump.*** A densitometer,† 2-channel recorder,‡ and computer† completed the instrumentation for obtaining cardiac output curves. Values obtained from the computer were verified at a later time by the method of Hamilton and associates¹¹ and found to be in agreement. Each cardiac output determination was made in duplicate. Peripheral resistance, mean transit time, and central blood volume were calculated from simultaneously recorded dye curves and intravascular pressure.

Heparinized arterial and venous blood samples were drawn anaerobically and pH, pO₂ and pCO₂ were determined by micro-electrode techniques.¶ Blood lactate levels were determined by the method of Barker and Summerson and pyruvate by the method of Friedmann and Haugen. Blood

volume was determined by simultaneous measurement of plasma volume using I¹²⁵-labeled albumin and red-cell mass using Cr⁵¹-labeled red cells. Three samples were taken over a period of an hour and the volume obtained by extrapolation to T₀ on semi-log paper.

Results

In all patients an attempt was made to evaluate effects of phenoxybenzamine on various hemodynamic and clinical parameters after conventional methods of therapy had proved to be of no further benefit. Prior to phenoxybenzamine administration, all patients received electrolyte and colloid solutions until the central venous pressure remained persistently above 10 mm. Hg. Acid base abnormalities and electrolyte disorders were corrected by intravenous fluid administration as required. In the four cases of septic shock the patients had received Metaraminol prior to transfer to the Shock Unit. All five patients were hypoxemic on admission, and three (Nos. 1, 2, 5) required tracheostomy and ventilator assistance and the other two required only nasal or mask oxygen in high volumes. Four patients (Nos. 1, 2, 3, 5) had been digitalized prior to receiving phenoxybenzamine and all septic patients received large (50 mg./Kg.) intravenous doses of corticosteroids without noticeable hemodynamic improvement. The four patients with sepsis had been receiving intravenous antibiotic agents prior to receiving phenoxybenzamine and in the absence of specific culture sensitivities, the regimen consisted of 2 Gm. chloramphenicol every 6 hours, either 2 Gm. Keflin or five million units of penicillin every 6 hours, and streptomycin 500 mg. every twelve hours. More appropriate antibiotics were instituted as sensitivity studies became available.

Criteria observed in selecting these patients to receive phenoxybenzamine were as follows: 1) clinical course of shock un-

* Statham 267 BC and 268B.

** Sanborn 7700 series.

*** Gilford Model 105-S.

† Gilford Model 103-1R, 104.

‡ Texas Instruments Recti-Writer.

¶ Instrument Laboratories Model 113.

responsive to adequate fluid therapy as measured by elevated central venous pressure; 2) signs of sympathetic overactivity, i.e., pallor, cold extremities, low pulse pressure, and decreased capillary filling; and 3) low cardiac index relative to estimated needs with normal or elevated peripheral resistance.

Absolute contra-indications to the use of a vasodilator were: 1) hypovolemia; 2) uncorrected electrolyte disturbance, acid-base disorder, or respiratory dysfunction; 3) evidence of acute myocardial infarction; and 4) inadequate monitoring facilities.

When the decision was made to administer phenoxybenzamine, base-line measurements were repeated and intravenous in-

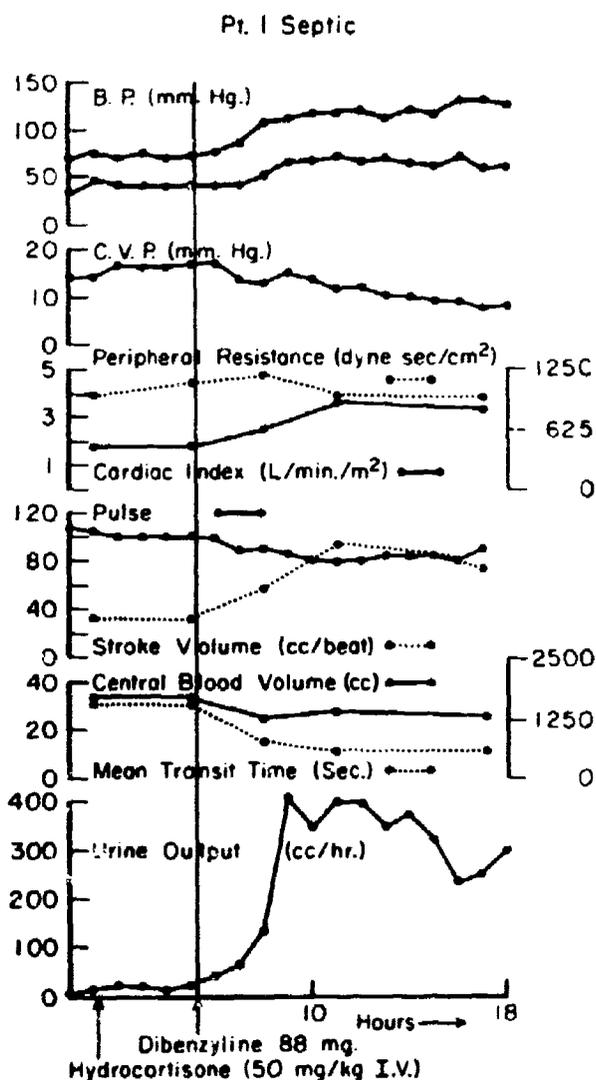


FIG. 1.

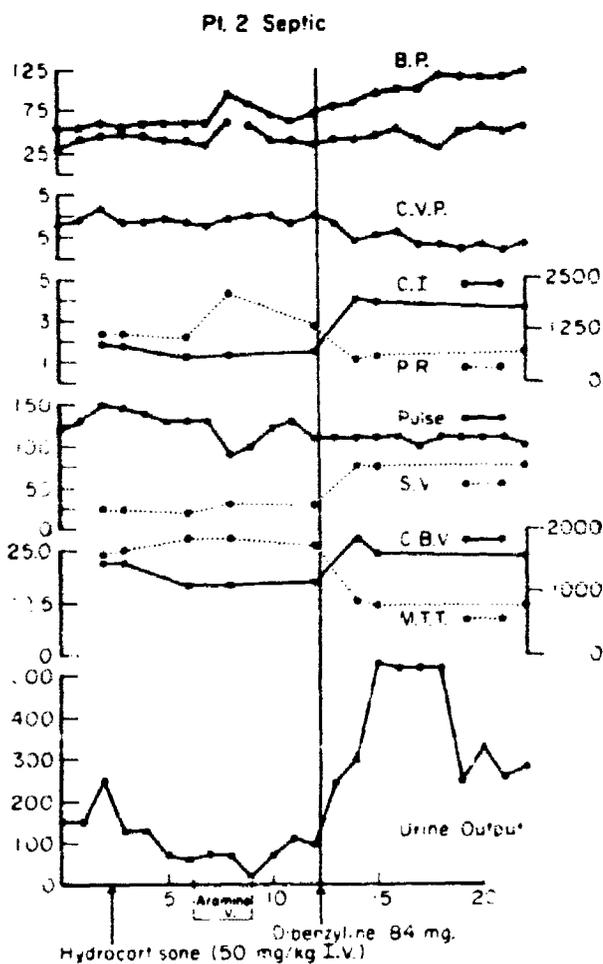


FIG. 2.

fusion of 200 cc. saline containing 1 mg./Kg. phenoxybenzamine (Dibenzyline^o) was administered over a 2-hour period. Clinical observations, hemodynamic measurements and laboratory studies were repeated serially and are presented in Figures 1 to 5.

Clinical Course. In all patients administration of phenoxybenzamine produced dramatic improvement within 2 hours of administration. Mentation improved and restlessness was alleviated. Vasoconstriction was relieved in the extremities, capillary fingernail perfusion improved, peripheral venous distention appeared and cyanosis was replaced by warm, pink skin. In patients who were oliguric prior to the administration of phenoxybenzamine, urinary output rose to normal levels within 2 hours.

^o Supplied by Smith, Kline and French Co.

Hemodynamics. Prior to administration of phenoxybenzamine all patients had a hemodynamic abnormality characterized by low cardiac output in spite of elevated central venous pressure (Figs. 1 to 5). Further administration of fluids did not increase cardiac output although filling pressure, as measured by central venous pressure rose. No patient had cardiac disease prior to the shock episode, but four (Nos. 1, 2, 4, 5) showed electrocardiographic patterns interpreted as ischemia during the course of shock.

In all patients the cardiac index increased notably following phenoxybenzamine due primarily to increase in stroke

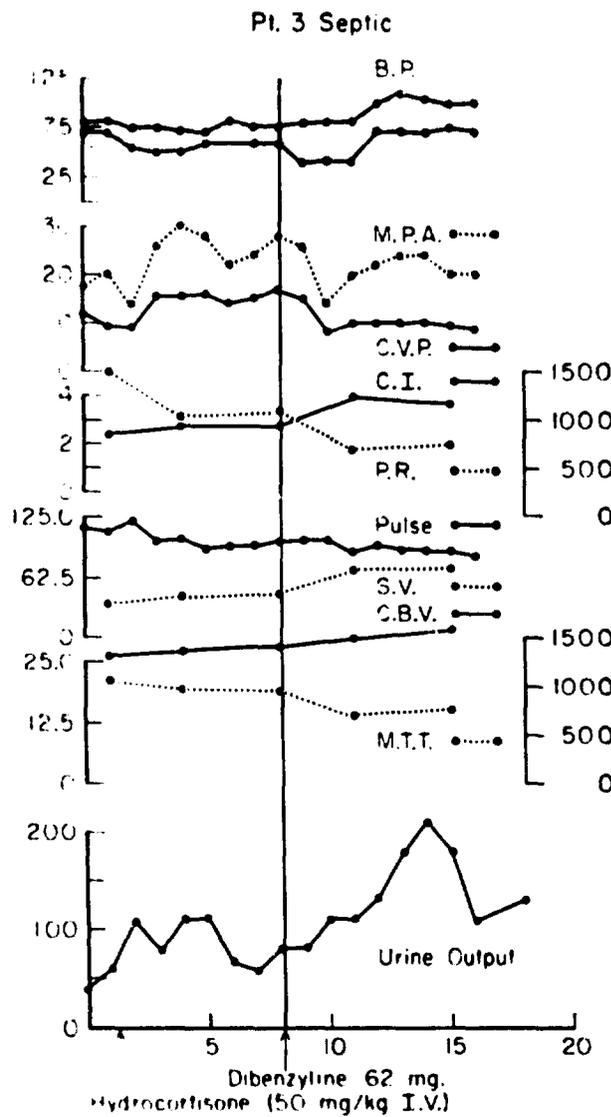


FIG. 3.

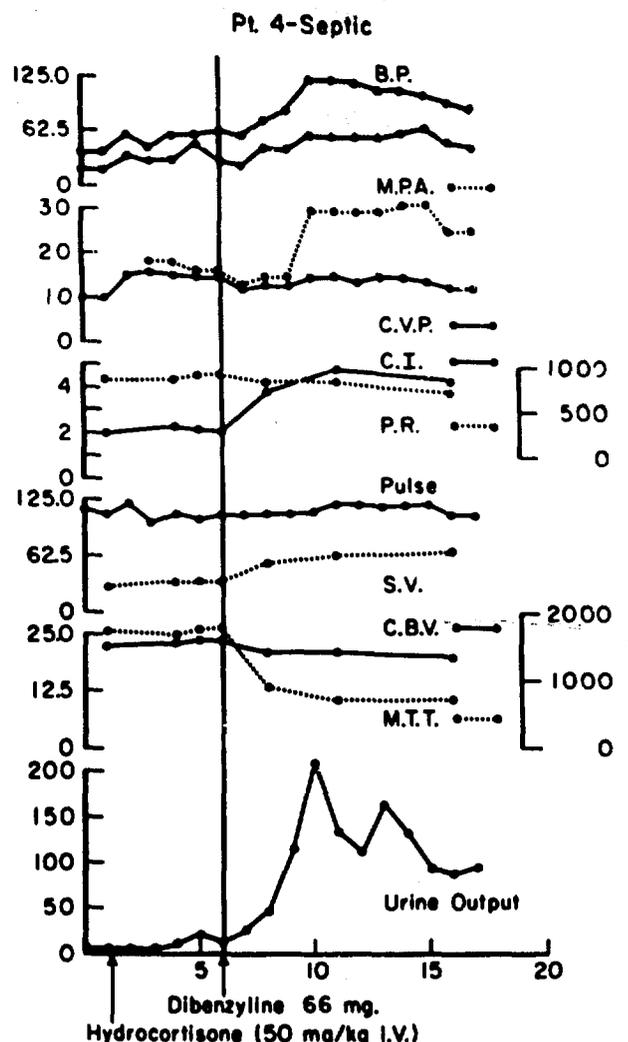


FIG. 4.

volume as the pulse rate either was unchanged or slowed. No patient had a drop in blood pressure as vasodilator was administered and in no case was rapid infusion of fluids required. Central venous pressure slowly dropped as cardiac performance improved and urine output increased. The mean transit time was shortened in every case following administration of vasodilator, but there was no consistency in changes observed in the central blood volume. Three patients in whom pulmonary artery pressures were monitored during phenoxybenzamine administration showed no changes in this parameter. This observation suggests that pulmonary resistance fell, but no calculation can be made as left atrial pressures were not measured and

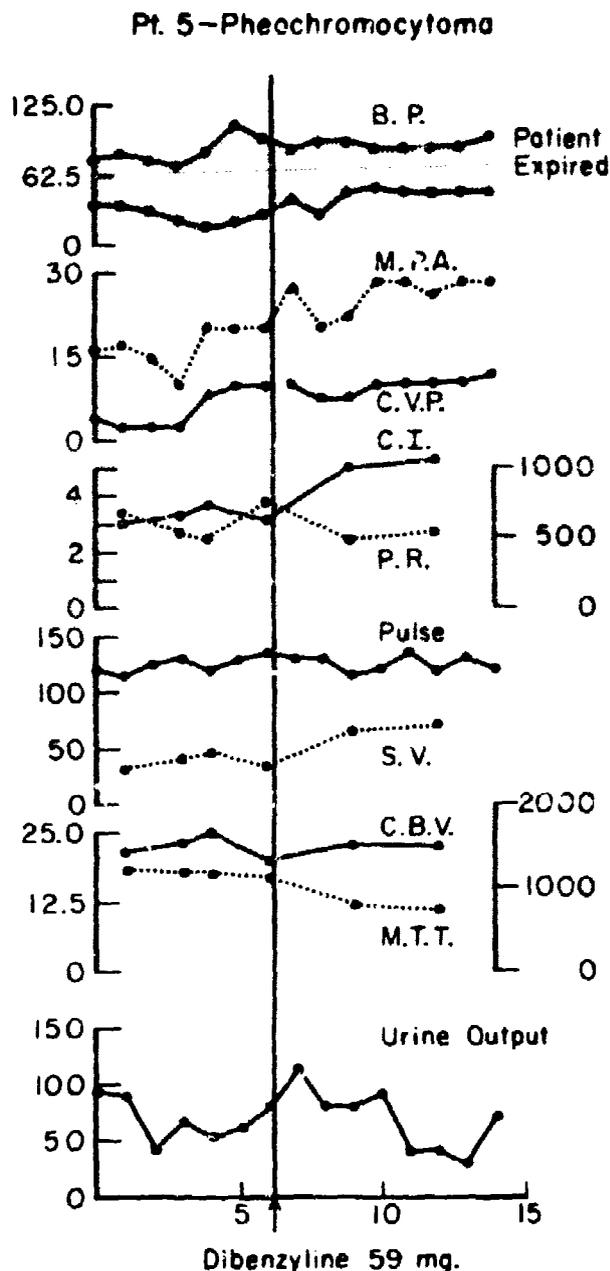


FIG. 5.

pulmonary wedge pressures are of questionable value in shock.

Laboratory Data. Table 2 summarizes biochemical findings. The most frequent abnormality was a compensated primary metabolic acidosis which progressed during periods of low tissue perfusion as metabolic products of anaerobic glycolysis accumulated. All patients had been vigorously treated prior to transfer and an electrolyte abnormality was found in only one patient (No. 2). Administration of phen-

oxybenzamine produced no biochemical derangements, as determined by laboratory studies, in any patient. Increased cellular perfusion was inferred from the progressive return to basal levels of lactate and calculated excess lactate in the septic patients.

Leukocytosis was found in four patients and in the fifth there was severe leukopenia. Blood volume determinations on admission are summarized in Table 3, and central venous pressure measurements recorded at the time the tracer isotope was injected are included.

Discussion

Our knowledge of the hemodynamic response to endotoxin in humans, when hypovolemia and cardiac failure can be excluded, is limited. In most reports there is a higher cardiac output in sepsis than in other forms of shock with a correspondingly lower total peripheral resistance.^{7-14, 28} The finding of both low and normal values for cardiac output in bacteremic shock is not a real contradiction as output would be more reduced in those more seriously affected. The finding of a normal basal cardiac index in febrile and hypotensive patients does not mean that cardiac output is normal in that situation. Whereas little more than resting basal cardiac output is required for recovery from a major operation,⁵ survival in sepsis and inflammation demands a sustained increase of cardiac output.¹ Udhoji and Weil concluded that the predominant circulatory defect in bacterial shock was profound reduction in cardiac output. These authors pointed out that in patients with a high basal cardiac output, e.g., cirrhotics, the fundamental circulatory defect that characterized shock was a critical reduction in effective blood flow which is not reflected in systemic cardiac output.²⁴ In this hyperkinetic group systemic flow is not available for effective perfusion of vital tissues but

TABLE 2. Biochemical Status on Admission to Shock Unit and Immediately Prior to Receiving Phenoxybenzamine

Pt. No.	Na	k	Cl	pH	HCO ₃	pCO ₂	pO ₂	Lactate per 100ml. pyruvate	Interpretation
1	136	4.0	100	7.45	22.5	34	50	25	Mild metabolic acidosis and respiratory alkalosis
1a	138	4.0	101	7.43	20	29	79*	70	As above
2	126	4.5	89	7.29	18.5	37	45	45 2.2	Metabolic acidosis with hyponatremia
2a	137	6.2	94	7.44	15	22	135**	51 4	Compensated metabolic acidosis
3	133	4.5	100	7.43	17	26	71	33 2.7	Compensated mild metabolic acidosis
3a	143	3.0	107	7.43	17	25	159*	56 2.5	As above
4	137	3.1	102	7.41	12	19	55	35 2.8	Compensated metabolic acidosis
4a	141	4.2	107	7.42	15	23	73*	42 2.2	As above
5	134	4.7	96	7.37	12	20	37	22 1.7	Partially compensated metabolic acidosis
5a	135	3.3	105	7.42	15	23	51**	30 1.6	Compensated metabolic acidosis

* Nasal oxygen.

** Tracheostomy with Engstrom respirator.

is shunted through arteriovenous communications. This explains the paradoxically elevated cardiac output found in cirrhotics with superimposed septic shock.

As MacLean pointed out, establishing a hemodynamic diagnosis for patients in shock provides valuable guides for therapy.^{17, 18} Gilbert earlier emphasized that three hemodynamic abnormalities are possible: 1) a deficit in work capacity of the heart; 2) a volume deficit; or 3) an abnormal state of the vascular bed.⁹ The data from our patients suggests that refractori-

ness to conventional therapy was associated with myocardial dysfunction as shock and low cardiac output persisted in the face of elevated central venous pressure and adequate cardiac filling pressure (Fig. 6).

The heart in shock has been neglected by many workers and little research has been directed toward function of the heart as compared to function of the peripheral circulation. Early papers of Wiggers²⁰ and Sarnoff *et al.*²² point out the importance of cardiac deterioration in the pathogenesis of shock. Later experimental data by Guyton

TABLE 3.

Pt.	WBC	Large vessel Ht	Total body Ht	Plasma volume (I ¹²⁵)	Red cell mass (Cr ⁵¹)	Total blood volume (% pred)	(mm.Hg) C.V.P.
1	32,100	35	27	5.81	2.10	7.91 (134%)	14
2	20,850	45	42	2.82	2.01	4.83 (83%)	11.5
3	16,000	37	38	3.09	1.95	5.04 (121%)	12
4	800	28	25	3.70	1.20	4.90 (108%)	16
5	22,000	65	53	2.03	2.29	4.32 (96%)	4

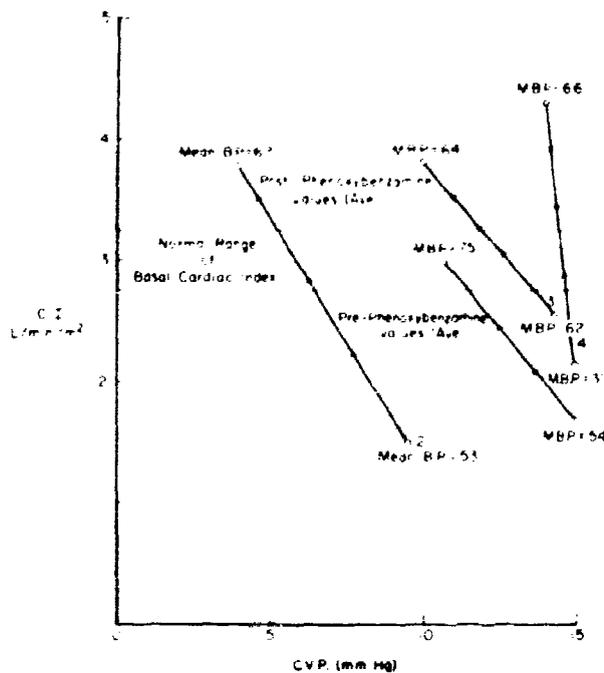


FIG. 6. Average cardiac indices and central venous pressures before and after administration of phenoxybenzamine.

and Crowell indicate that the heart might be the primary failing organ and damage to the peripheral circulation might be of secondary importance.¹⁰ Clinical studies of Wilson *et al.*²⁷ and MacLean *et al.*¹⁸ stressed the frequency of a cardiac deficit as the most important hemodynamic abnormality in later stages of shock and demonstrated the salutary effects of therapy which increased performance of the heart. Wilson's group used phenoxybenzamine and MacLean's patients were treated with isoproterenol.

There have been few reports on the use of phenoxybenzamine in man. Eckenhoff and Cooperman reported the use of this agent in 25 patients and that their poorest result was in the treatment of shock.⁶ Theirs was a heterogeneous group of patients who had been in shock for long periods and received phenoxybenzamine as a last resort. Few hemodynamic parameters were measured and no criteria were used in administering the drug. Wilson, Jablonski and Thal reported results of administering phenoxybenzamine to 19 patients with advanced

clinical shock from a variety of causes.²⁷ Although this also was a heterogeneous group, all of whom had failed to respond to vigorous standard therapy, these authors concluded that the over-all effects of phenoxybenzamine appeared to be beneficial. This report contained hemodynamic measurements and most patients had a fall in central venous and arterial blood pressure with a rise in cardiac output.

Four cases presented here constitute a homogeneous group of young, previously healthy adults who developed shock attributable solely to sepsis. In all cases there was a dramatic response to administration of intravenous phenoxybenzamine and the primary action of the drug appeared to be the restoration of functional capacity in the myocardium (Fig. 6). The fifth case was unique; shock secondary to excessive catecholamines secreted by bilateral pheochromocytomas. In spite of appropriate antiadrenergic therapy with phenoxybenzamine this patient had a rapid downhill course and died of fulminant pulmonary congestion. The mechanism of action of phenoxybenzamine is not well defined, but it is known that it acts directly and specifically on alpha-adrenergic cells and its blockade is therefore selective for vasoconstrictor components of the sympathetics. It has been stated that most alpha receptor-blocking drugs induce cardiac stimulation because the fall in systemic blood pressure accompanying systemic vasodilation initiates a reflex tachycardia, and sympathetic nerve pathways to the heart are uninfluenced by these drugs.³ One alpha-adrenergic drug, phentolamine, has a direct stimulating action on the heart which supplements the reflex mechanism responsible for the increase in cardiac output.³ Preliminary animal studies suggest that phenoxybenzamine may also have direct action on the myocardium of the dog in endotoxin shock.² The pattern of action of vasodilation and cardiac stimulation raises the

question as to which of these two actions is more important. In patients we studied there was no drop in blood pressure or increase in pulse rate following administration of phenoxybenzamine but cardiac indices rose in spite of falling central venous pressure. The implication is that myocardial dysfunction played a major role in preventing recovery and recovery was not likely unless something could be done to restore the heart to more normal function. On the basis of our studies we believe that phenoxybenzamine improved cardiac function and increased cardiac performance. Three modes of action appear to be possible: 1) direct inotropic action on the myocardium; 2) vasodilating effect on the coronary vessels and myocardial microvasculature; and 3) relief of post-capillary pulmonary vasoconstriction with increased venous return to the left heart.

Studies are currently underway to elucidate further the manner in which phenoxybenzamine affects the heart in septic shock.

Summary

A series of young patients with well defined diagnoses and refractory clinical shock have been studied hemodynamically. When conventional methods of therapy failed to correct hemodynamic deficits phenoxybenzamine was administered and physiologic parameters were carefully monitored. The pattern of response suggests that phenoxybenzamine improved cardiac function directly and thereby improved tissue capillary perfusion.

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